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Atherosclerosis in Patients with Rheumatoid Arthritis

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Abstract

Both Rheumatoid Arthritis (RA) and atherosclerosis are complex polygenic diseases. Previous studies have demonstrated that patients with RA are associated with up to 60% increased risk of cardiovascular disease related death. Nonetheless, the increased cardiovascular morbidity and mortality in patients with RA cannot be entirely explained by traditional risk factors, and likely to be multifactorial. The present article reviews the data supporting the association of RA with cardiovascular risk factors, possible mechanism for developing atherosclerosis and evaluates the potential strategies that may prevent premature atherosclerosis in these patients.

Keywords: Rheumatoid Arthritis (RA); Atherosclerosis; Cardiovascular disease

Introduction

Rheumatoid Arthritis (RA) is a chronic inflammatory disease, which affects 0.51% of the population in the world [1-3]. RA is characterized by a systemic inflammatory state, involving several organs, including joints, skin, eyes, lung and blood vessels [4]. Patients with conditions such as RA are associated with an increase mortality compared with the general population [5]. A major part of the excess mortality has been attributed to cardiovascular disease (CVD) [5,6]. The results of a recent systematic review showed that RA is associated with a 60% increase in the risk of CVD-related death [7]. In particular, inflammation in RA is now considered as an independent risk factor for the development of atherosclerosis [8]. Both RA and atherosclerosis are complex polygenic diseases with shared disease mechanism. There is increasing evidence that chronic inflammation and immune dysregulation contributes to accelerated atherogenesis and plays a role in all stages of atherosclerosis (i.e., atherogenesis, atheroma progression, and the development of thrombosis) [7]. Further, the increased cardiovascular morbidity and mortality in patients with RA cannot be entirely explained by traditional risk factors, such as type 2 diabetes mellitus, Metabolic Syndrome (MetS) and smoking habit. This article reviews the data supporting the association of RA with CVD, the possible mechanism for atherosclerosis, and discusses potential strategies for the prevention of atherosclerosis in such patients.

Mortality and mortality of RA is related to atherosclerosis

Large epidemiological studies from the last few decades have confirmed that patients with RA are 60% more likely to suffer a CV event than subjects from the general population [7]. The major complication in patients with RA is the development of cardiovascular events due to accelerated atherosclerosis. A recent Dutch, cross-sectional study found that age- and gender-adjusted odds ratios for CV diseases derived from these cohorts were 3.1 for patients with RA. Further, up to 13% non-diabetic RA patients developed CVD (coronary, cerebral and peripheral arterial diseases) [9]. Multiple studies have confirmed that the excess mortality in RA is largely attributed to CV death. A recent meta-analysis of 24 studies showed a 50% increased risk of CV death overall [10]. RA patients have a 2 to 3 fold risk of myocardial infarction, a 2 fold risk of congestive heart failure, a 2 increase risk of sudden death and a 1.7 fold increased risk of strokes [11-14]. Accordingly, clinicians should be aware of the high risk and provide close surveillance of CVD in patients with RA.

Subclinical Atherosclerosis

Carotid intima-media thickness

An approach to assess the presence and extent of subclinical atherosclerosis is carotid ultrasonography. In the general population, carotid ultrasound has been used for cardiovascular risk stratification; Intimal-Medial Thickness (IMT) and plaque are associated with clinical CVD and have independent prognostic value for such CV events [14]. In 2 studies of Asian patients [15,16] and in a study from Poland [17], carotid IMT was increased in patients with RA compared with matched controls. In addition, patients with RA had a similar carotid IMT and prevalence of carotid plaque as with age- and gender-matched patients with type 2 diabetes mellitus. The result thus suggested that both diseases contribute equally to the development of premature atherosclerosis [18]. A meta-analysis was performed involving 22 studies to estimate the overall mean carotid IMT difference between RA and control groups [19]. In 17 of the studies, patients with RA had a statistically significantly greater carotid IMT. The overall mean carotid IMT difference was 0.09 mm, indicated an approximately 15% increased cardiovascular risk [20]. However, this was not confirmed by a study from the United States, showing no significant difference in carotid IMT and carotid plaque between patients with RA and control [21]. Nonetheless, carotid IMT was correlated positively with inflammatory markers both in patients with RA and controls, suggesting that systemic inflammation played a significant role in the development of atherosclerosis.

The presence of carotid plaques is a more reliable predictor of cardiovascular events than IMT [22]. In a cross-sectional study of 98 patients with RA, Salmon and Roman [23] demonstrated that the presence of carotid atherosclerotic plaques was greater than controls (44% vs. 15%, $p<0.01$). The same result was similarly shown by and Stamatelopoulos and colleagues [18] (48% vs. 10%, $p<0.01$). The

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clinical importance for the presence of carotid plaque, but not carotid IMT, was demonstrated by a study involving 105 patients with RA, that demonstrated patients with bilateral carotid plaques were associated with a worse CVD event survival (Hazard ratio = 6.31) [24]. These result confirmed that RA is strongly associated with atherosclerosis development in the carotid arteries that could explain for the high stroke incidence in these patients.

Coronary artery calcification

Coronary Arterial Calcification (CAC), as a subclinical measure of atherosclerosis, measured by Computed Tomography (CT), is closely associated with the degree of atherosclerotic plaque [25], and is strongly predictive of cardiovascular events [26,27]. In a report by Chung and colleague, patients with early RA or established RA had a significantly higher prevalence of CAC than non-RA controls (43% vs. 61% vs. 38%, respectively, p=0.016) [28]. Moreover, patients with longstanding RA have been shown to be associated with a higher CAC, suggesting that disease duration may be an important factor related to coronary atherosclerosis [29]. In a study by Giles et al., increasing severity of RA was associated with a high prevalence and extent of coronary calcification, irrespective of gender and age. Interestingly, these association was attenuated after adjusting for IL-6, thus suggest that systemic inflammation was important to the development of coronary atherosclerosis [28]. Another study by Wang and colleagues has further demonstrated that patients with RA had earlier onset, more diffuse arterial calcification over multiple vascular beds and more preferential involvement of thoracic aorta, rather than coronary artery compared with control [29].

Microcirculation disorder

The endothelium is the innermost lining of the vasculature and its integrity is crucial to maintain vascular hemostasis. Damage to the endothelium can cause endothelial dysfunction, which is an early indicator for CVD [30]. As endothelial dysfunction may occur differentially in different vascular beds, in particular, microvascular dysfunction may occur in addition to macrovascular dysfunction. A study involving 99 RA patients evaluated the relation between microvascular function using laser Doppler imaging, with macrovascular vasodilatory function [31]. It was shown that both microvascular and macrovascular endothelial function were independent of each other in patients with RA, suggesting differential regulation of endothelial function in these two vascular beds. Indeed, microvascular dysfunction has been previously described in patients with RA [32,33]. In 65 female RA patients, cutaneous microcirculatory function, assessed by laser Doppler imaging, was reduced compared with controls [34]. Similarly, a study by Datta et al. [33] demonstrated that among 8 RA patients, cutaneous microvascular function was impaired and subsequently improved following treatment of disease [35]. Another recent study demonstrated 12/18 RA patients had myocardial ischemia by dobutamine stress contrast echocardiography. Interestingly, 8 of these patients underwent invasive coronary angiogram of which 4 had normal coronary vessels, 2 had non-flow limiting coronary lesions and the remaining had significant coronary atherosclerosis. This results suggested that microvascular abnormalities may account for myocardial ischemia as evidenced by absence of significant coronary occlusion in a significant number of patients [36]. Accordingly, these studies highlighted that atherosclerosis is not limited to plaque formation in large conduit vessels but also disturb function in smaller resistance vessels, that is key in regulating tissue perfusion, including myocardial perfusion.

Mechanism of Premature Atherosclerosis

The pathogenesis of atherosclerosis is likely multifactorial, including clustering of traditional cardiovascular risk factors, inflammatory mediated and genetic factors (Figure 1) [37].

The cardiovascular risk factors for atherosclero Traditional risk factors

Traditional risk factors for vascular disease, such as smoking, hypertension, diabetes and hyperlipidemia are important, but cannot fully account for, the increased risk of CVD in RA [38]. In a study by Chung et al., 197 patients with RA were compared with 274 frequency-matched control subjects [39]. It was found that 80% of patients with RA and 81% of control subjects had at least 1 modifiable traditional cardiovascular risk factor. Hypertension was more prevalent in the RA group (57%) than in controls [42%, p=0.001]. However, there were no statistically significant differences in the frequency of diabetes, elevated body mass index, smoking, intermediate-high 10-year coronary heart disease risk, or elevated LDL in patients with RA versus controls. Moreover, rates of newly identified diabetes, hypertension, and hyperlipidemia were similar in RA patients versus controls.

(ι) **Metabolic syndrome:** Metabolic syndrome (MetS) is a cluster of traditional risk factors (including hypertension, diabetes, dyslipidemia and central obesity) that increase the risk of cardiovascular events. The most commonly used definitions for the diagnosis of MetS include the WHO criteria and the National Cholesterol Education Program Adult Treatment Panel (NCEP) III criteria. Both of these definitions involve the assessment of fasting glucose, dyslipidemia, hypertension and central obesity. Indeed, MetS is a common presentation in patients with rheumatic diseases and represents an important risk for developing atherosclerosis.

A study by da Cunha et al. involving 283 patients with RA and 226 controls demonstrated that the risk of having MetS was significantly higher in RA patients than controls [odds ratio (OR) =1.9, p<0.01] and was associated with disease activity [40]. Further, MetS has been shown to be more prevalent in patients with long-standing RA or early RA than in non-RA controls (WHO criteria: 42% versus 31% versus 11%, respectively, P<0.001; NCEPIII criteria: 42% versus 30% versus 22%, p=0.03) [41]. Another study evaluated the prevalence of MetS in 200 patients with RA (mean age of 63, 147 female) and 400 age-matched

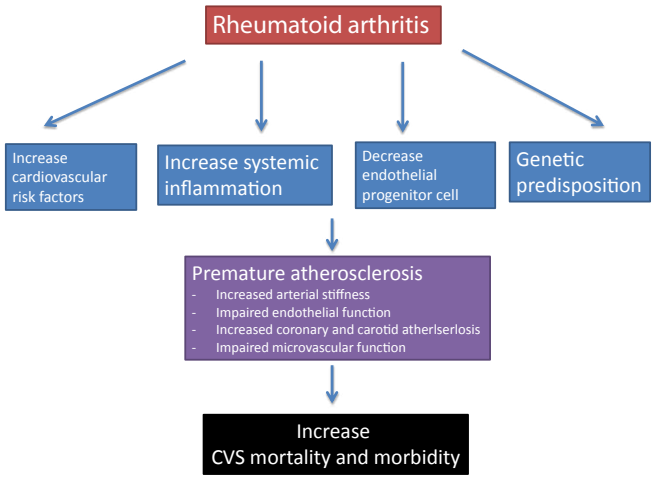

Figure 1: Potential pathogenesis of premature atherosclerosis in patients with rheumatoid arthirits.

non-RA controls in the Mediterranean region. Although the overall prevalence of MetS was similar between both patient groups (44% versus 41%, p=0.5), those with RA who had MetS were more likely to have high RA disease activity (DAS28 >3.2) than those without MetS [42]. In addition, individual cardiovascular risk factors contributed to carotid IMT thickness in a study that involved 631 patients with RA [43]. Data from the Consortium of Rheumatology Researchers of North America registry demonstrated that increased markers of severity of RA, in addition to conventional CVD risk factors, were associated with an increase in cardiovascular risk. In particular, patients with absence of risk factors or markers of RA severity did not develop any cardiovascular events. In contrast, patients with at least two traditional CVD risk factors and three or more markers of RA severity had an incidence rate of 7.47 (per 1,000 person-years) [44]. These data thus suggest that conventional CVD risk factors and MetS are both associated with the development of premature atherosclerosis in RA.

Endothelial progenitor cells

Atherosclerosis is an inflammatory condition which starts as a "response to injury" favoring endothelial dysfunction which is associated with increased expression of adhesion molecules, pro-inflammatory cytokines, pro-thrombotic factors, oxidative stress upregulation and abnormal vascular tone modulation. Endothelial dysfunction in rheumatic autoimmune diseases involves innate immune responses, including macrophages and dendritic cells expression of scavenger and toll-like receptors for modified or native LDL as well as neutrophil and complement activation, and dysregulation of adaptive immune responses, including proliferation of autoreactive T-helper-1 lymphocytes and defective function of dendritic and regulatory T cells [45]. As previously pointed out by Kitas and Gabriel, classic CV risk factors are important but not sufficient to explain all of the CV excess risk found in RA [46]. Endothelial dysfunction is an early step in the atherogenesis process of RA. More experiments have showed that microvascular endothelial function is a better predictor of CV outcome than macrovascular endothelial function in patients with RA [47,48].

Vasculogenesis is the generation of vessels from Endothelial Progenitor Cells (EPCs). Vasculogenesis may also be linked to atherosclerosis in RA [49]. Stimulation of EPCs and vasculogenesis may be beneficial to prevent and manage atherosclerosis related to arthritis [50].

The study by Yiu et al. demonstrated that RA patients with coronary atherosclerosis have significantly lower levels of $CD133/KDR^+$ and $CD133^+$ EPC than those without. In addition to older age, lower levels of circulating $CD133/KDR^+$ EPC also predicted occurrence of coronary atherosclerosis in RA patients [51]. The result of this study thus confirmed that EPCs is closely associated with coronary atherosclerosis in this group of patients. While measures that may increase EPCs and provide protection for premature atherosclerosis would however require future studies for evaluation.

Chronic inflammation and immune dysregulation of RA and atherosclerosis

Conventional cardiovascular risk factors may not fully account for the difference in risk of CVD between patients with RA and the general population. Systemic inflammation is one of the pivotal pathogenetic principles in atherogenesis and progression of atherosclerosis. Accordingly, RA-related systemic inflammation, may contribute to the observed gap [52].

In patients with RA, a raised baseline C-reactive protein (CRP) level is an independent predictor for cardiovascular mortality, which means reduction of inflammatory activity may reduce cardiovascular morbidity and mortality [53]. Further, inflammatory disorders, characterized by high levels of CRP, can develop a secondary immune cell activation, which may result in atherogenesis [54]. In addition, studies have demonstrated that inflammatory related markers such as lipoproteins, ox-LDLs [55], NO [55], TNF-a [56], RANKL [57], CD40L [58], IL-18 [59], MMP-9 [60], MCP-1[61], insulin [45], EPCs [51] in atherosclerosis are altered in patients with RA. These evidences thus support the theory that systemic inflammation plays a crucial role in the pathogenesis of CVD in patients with RA.

Genetic influence in the development of CV disease in patients with RA

Both RA and atherosclerosis display a strong genetic component of susceptibility [52]. RA has an estimated heritability of up to 60% [62] and CV disease in the general population of up to 30–60% [63]. Besides, a specific genetic background may contribute to the development of both diseases. The chemokine CCL21 has also been implicated in the pathogenesis of both RA and atherosclerosis [34,35]. A polymorphism from this gene (rs2812378) was associated to a higher CV and all-causes mortality risk, in a UK chronic arthritis, including RA, cohort.

The plasminogen activator inhibitor type 1 (PAI-1) is the primary physiologic inhibitor of plasminogen activation in blood [64]. PAI-1 overexpression may compromise normal fibrin clearance mechanisms and promote pathological fibrin deposition and thrombotic events. A polymorphism of this gene, located in the promoter region (at starting position –675, 4G/5G), has previously been associated to CV disease and venous thrombotic episodes [65] in the general population. In patients with RA, this variant, together with TNFRII and FXIIIA, have also been associated with CVD in a cohort of Sweden patients [66].

Atherosclerosis and Rheumatoid Arthritis Therapies

Corticosteroids

Corticosteroids are often used in the treatment of SLE, RA, and other inflammatory disorders. High dose treatment with corticosteroids has adverse effects on the cardiovascular system, including endothelial dysfunction, hypertension and dysregulated glucose metabolism [67]. In a population-based cohort (n=603), Rheumatoid Factor (RF)-positive patients were at increased risk of cardiovascular events following exposure to glucocorticoids, but not RF-negative patients [68]. The influence of low-dose prednisolone on atherosclerosis, endothelial function, and risk factors for atherosclerosis in patients with early RA was studied by Hafström [69,70]. These studies demonstrated that low-dose prednisolone (less than 7.5 mg daily) did not influence endothelial function and atherosclerosis in patients with RA. The mechanisms causing the potential interaction between corticosteroid exposure and premature atherosclerosis should be evaluated in future researches.

Statin

Statins (3-hydroxy-3-methylglutarylcoenzyme-A reductase inhibitors) reduce CVD morbidity and mortality in at-risk patients [71]. The anti-inflammatory and immunomodulating effects of statins include suppression of leukocyte cytokine release, reduced MHC class II expression and reduced production of reactive oxygen species [72]. A recent population-based longitudinal study demonstrated that statin discontinuation is associated with an increased risk of CVD related death (Relative risk=1.79) [73]. Apart from reducing lipid levels, treatment with statin in patients with RA may also have a modest but clinically useful effect on arthritis. Atorvastatin has also been shown to

	Patient number	Type of study	Treatment	Surrogate markers	Results
Statin					
Van Doornum et al. [74]	N=29 Age=55	Prospective observational	Atorvastatin 20mg daily for 12 weeks	AI	AI improved 34.1➔ 30.6% (P<0.01)
Mäki-Petäjä et al. [75]	N=20 Age=58	Prospective observational	Simvastatin 20mg or ezetimib 10mg daily, each for 6 weeks	PWV FMD	PWV and FMD significantly improved by both medications.
Hermann et al. [76]	N=20 Age=57	Double blind randomized	Simvastatin 40mg daily for 4 weeks	FMD	FMD improves in patients with statin compared with placebo 5.5% vs. 3.8% (P=0.02)
Biologics therapy					
Hürlimann et al. [88]	N=11 Age=46	Post-hoc analysis from a randomized controlled trial	Infliximab for 12 weeks	FMD	FMD improved from 3.2% ➔4.1% (P=0.02)
Wong et al. [89]	N=26	Prospective observational	Infliximab for 54 weeks	PWV cIMT	PWV significantly improved but not cIMT
Van Doornum et al. [91]	N=14 Age=55	Prospective observational	Etanercept (N=7) Adalimumab (N=6) IFx (N=1) for 6 weeks	AI	AI remained unchanged 29.1% ➔30.1% (P=0.50)
Tam et al. [93]	N=40 Age=53	Randomized open-label study	MTx Alone (N=20) MTx + IFx (N=20) for 6 month	AI PWV	MTx + early IFX improved PWV than MTx alone in early RA patients with active disease.
Mäki-Petäjä et al. [94]	N=17 Age=58	Prospective observational	Adalimumab (N=12) Etanercept (N=5) in 8 weeks	^{18}F-FDG-PET	Reduction in TBR_{max} from 2.02 to 1.90 (P=0.03)
Protogerou et al. [96]	N=16 Age=44	Prospective observational	Tocilizumab for 6 months	PWV FMD	FMD improved from 3.3% ➔ 5.2%. PWV decreased from 8.2 m/s ➔ 7.0 m/s
Kerekes et al. [99]	N=5 Age=42	Prospective observational	Rituximab for 2 doses	cIMT FMD	cIMT improved in 3/5 patients by 16 weeks FMD improved in 4/5 patients by 16 weeks

Abbreviations: ^{18}F-FDG-PET = ^{18}F-fluorodeoxyglucose positron emission tomography; AI = arterial stiffiness; ccIMT= carotid intima media thickness; FMD = flow mediated dilatation; IFx =Infliximib; MTx = Methotrexate, TBR_{max} = arterial maximum target-to-background ratio

Table 1: The effect of statin and biologics therapy to prevent premature atherosclerosis in patients with rheumatoid arthritis.

reduce arterial stiffness in patients with RA and high disease activity [74] (Table 1). Further, it was shown that aortic PWV and flow mediated dilatation (FMD) was significantly improved upon treatment with atorvastatin or ezetimib [75]. In a study by Hermann et al., it was shown that statin therapy improves vascular function measured by FMD [76]. Another study involving 50 RA patients were randomized in a double-blind placebo-controlled trial in receiving 10 mg rosuvastatin (n=24) or placebo (n=26) [77]. It was shown that rosuvastatin has a modest anti-inflammatory effect in patients with RA and low disease activity in terms of reduction in DAS and fibrinogen level, but not arterial stiffness or carotid IMT. Accordingly, statin-related reduction in inflammatory biomarkers provided the rationale for a randomized controlled trial of atorvastatin for treatment of synovitis in RA (the Trial of Atorvastatin in Rheumatoid Arthritis [TARA]) [78].

Methotrexate and atherosclerosis

Methotrexate (MTX) is the first-choice DMARD in patients RA. Its mechanisms of action are diverse and complex but in the doses used to treat RA, its actions are likely to be anti-inflammatory. The anti-inflammatory effects of MTX in RA may thus prevent premature development of atherosclerosis. In a cohort of 1240 patients with RA, it was shown the MTX provided survival benefit mainly by reducing cardiovascular mortality (relative risk=0.3) during a mean of 6 years follow up [79]. Similarly, other studies have demonstrated that MTX therapy is associated with a reduction of cardiovascular morbidity and mortality, ranging from 15% to 85% [80-82]. In addition, 2 small studies have shown statistically significant reductions in carotid IMT with combination MTX plus chloroquine therapy [83] and combination MTX plus prednisolone therapy [84] but have not assessed the effect of MTX alone. However, the beneficial effect of MTX therapy in the preventing preclinical atherosclerosis was not confirmed in another study [15]. Nonetheless, randomized study to evaluate the cardiovascular protective effect of MTX in patients with RA would be required.

Biologics therapy and atherosclerosis

The cytokine tumour necrosis factor α (TNFα) is key in the pathogenesis of RA [85]. Theoretically, anti-TNFα will, by reducing inflammation and improving arthritis, may also decrease the burden of CVD. Accordingly, a number of studies using anti-TNFα, such as infliximab, etanercept, adalimnumab, attempted to evaluate its cardioprotective in patients with RA. In a prospective observation study by Dixon et al., it was shown that patients with RA who respond to anti-TNFα therapy (n=5877) had a lower risk of myocardial infarction (relative risk=0.38) compared with non-responders (n=1638) [86]. In contrast, in a recent cohort study (n=6000), neither treatment with nor response to anti-TNFα reduced the risk of acute coronary syndrome within the first year of diagnosis of RA, which may be explained by the differences in the burden of disease [87].

In an early report, Hürlimann et al. demonstrated that anti-TNFα therapy improves endothelial function in patients with RA (Table 1) [88]. In a post hoc analysis of longitudinal data from a randomized placebo controlled study also showed that infliximab therapy was associated with an improvement of arterial stiffness as measured by pulse wave velocity (PWV), but not carotid IMT and carotid artery plaque, in patients with RA (n=26) [89]. Further, 1-year treatment with anti-TNFα therapy has been shown to improve both PWV and carotid IMT in patients with inflammatory arthropathies [90]. However in another study, despite significant reduction in synovitis and inflammatory markers, 6 weeks of anti-TNF α therapy did not improve arterial stiffness [91]. The effect of anti-rheumatic treatment on microvascular endothelial function in 51 patients with active RA and no previous history of cardiovascular disease was assessed by Galarraga [92]. It was found that both endothelium-dependent and independent responses did not improve significantly after treatment with biologics or methotrexate therapy. However, patients who responded to anti-rheumatic therapy (n=31) showed significant improvement in both

endothelium-dependent and independent responses. This study thus suggested that tight and aggressive control of RA disease activity may protect CVD in addition to joint damage and disability. In a recent open-label study in patients with early RA, PWV was compared between methotrexate (MTX) alone and MTX plus infliximab (n=20 each arm) [93]. The result showed that MTX plus infliximab significantly reduced PWV compared with MTX alone. A more recent study further demonstrated that aortic inflammation can be reduced by anti-TNFα detected by aortic (18)F-fluorodeoxyglucose positron emission tomography with computed tomography coregistration [94]. Moreover, the reduction of aortic inflammation is associated with concomitant improvements in endothelial function, inflammatory markers and aortic stiffness. These studies thus suggested that use of anti-TNFα therapy improves cardiovascular surrogate markers and protect the development of premature atherosclerosis in RA patients.

In addition to anti-TNFα, interleukin (IL)-6 is also an important factor that regulates the immune response, inflammation and hematopoiesis. Blocking IL-6 actions by tocilizumab, a humanized antibody has been shown to be therapeutically effective in treatment of RA or rheumatic disease [95]. As a result, effective IL-6 receptor inhibition may provide protection to cardiovascular system in RA patients. A recent study demonstrated that in RA female patients, the use of tocilizumab improves both endothelial function and arterial stiffness (Table 1) [96]. Further, rituximab, a chimeric human/mouse monoclonal antibody directed at the CD20 antigen expressed on mature B and pre-B cells, has been approved for treatment of moderate to severe RA, with MTX, in patients who have inadequate response to at least one anti-TNFα inhibitor [97]. In a study involving 49 RA patients, the atherogenic index significantly improved (~9%) after 6 months treatment with rituximab, indicating the beneficial effects on lipid profile along with improvement of disease activity [98]. Study involving small number of RA patients have also demonstrated that rituximab improves carotid atherosclerosis and endothelial function (Table 1) [99]. These data suggest the potential benefit of novel biologics in preventing CVD in RA patients.

Conclusion

Clinical and basic science studies consistently demonstrated that RA is a condition that accelerates atherosclerosis. Both surrogate markers for atherosclerosis and epidemiology studies have confirmed the increased risk of CVD in patients with RA. The pathogenesis of premature atherosclerosis is likely multifactorial and cannot be entirely explained by traditional risk factors. Importantly, therapies that control the disease activity hold promise in preventing the development of CVD in this group of patients. Future large randomized studies are thus important to address and define the therapeutic option in the prevention of cardiovascular complication.

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